Tofranil-PM®

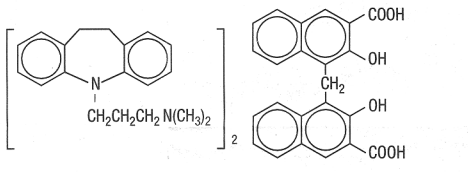
imipramine pamoate
Capsules of 75 mg
Capsules of 100 mg
Capsules of 125 mg
Capsules of 150 mg

For oral administration

Prescribing Information

DESCRIPTION

Tofranil-PM, imipramine pamoate, is a tricyclic antidepressant, available as capsules for oral administration. The 75-, 100-, 125-, and 150-mgcapsules contain imipramine pamoate equivalent to 75, 100, 125, and 150 mg of imipramine hydrochloride. Imipramine pamoate is 5-[3(dimethylamino)propyl]-1 0,11 -dihydro-5H-dibenz[b,f]azepine 4,4'-methylenebis-(3-hydroxy-2-naphthoate) (2:1), and its structural formula is



Imipramine pamoate is a fine, yellow, tasteless, odorless powder. It is soluble in ethanol, in acetone, in ether, in chloroform, and in carbon tetrachloride, and is insoluble in water, Its molecular weight is 949.21.

Inactive ingredients. D&C Red No. 28, FD&C Blue No. 1, FD&C Yellow No. 6, D&C Yellow No. 10 (100 mg and 125 mg tablets only), gelatin, magnesium stearate, parabens, silicon dioxide, sodium lauryl sulfate, starch, talc, and titanium dioxide.

CLINICAL PHARMACOLOGY

The mechanism of action of imipramine is not definitely known. However, it does not act primarily by stimulation of the central nervous system. The clinical effect is hypothesized as being due to potentiation of adrenergic synapses by blocking uptake of norepinephrine at nerve endings.

INDICATIONS AND USAGE

For the relief of symptoms of depression. Endogenous depression is more likely to be alleviated than other depressive states. One to three weeks of treatment may be needed before optimal therapeutic effects are evident.

CONTRAINDICATIONS

The concomitant use of monoamine oxidase inhibiting compounds is contraindicated. Hyperpyretic crises or severe convulsive seizures may occur in patients receiving such combinations. The potentiation of adverse effects can be serious, or even fatal. When it is desired to substitute Tofranil-PM in patients receiving a monoamine oxidase inhibitor, as long an interval should elapse as the clinical situation will allow, with a minimum of 14 days. Initial dosage should be low and increases should be gradual and cautiously prescribed.

The drug is contraindicated during the acute recovery period after a myocardial infarction. Patients with a known hypersensitivity to this compound should not be given the drug. The possibility of cross-sensitivity to other dibenzazepine compounds should be kept in mind.

WARNINGS

Extreme caution should be used when this drug is given to patients with cardiovascular disease because of the possibility of conduction defects, arrhythmias, congestive heart failure, myocardial infarction, strokes, and tachycardia. These patients require cardiac surveillance at all dosage levels of the drug; patients with increased intraocular pressure, history of urinary retention, or history of narrow-angle glaucoma because of the drug's anticholinergic properties; hyperthyroid patients or those on thyroid medication because of the possibility of cardiovascular toxicity; patients with a history of seizure disorder because this drug has been shown to lower the seizure threshold; patients receiving guanethidine, clonidine, or similar agents, since imipramine pamoate may block the pharmacologic effects of these drugs; patients receiving methylphenidate hydrochloride. Since methylphenidate hydrochloride may inhibit the metabolism of imipramine pamoate, downward dosage adjustment of imipramine pamoate may be required when given concomitantly with methylphenidate hydrochloride.

Since imipramine pamoate may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as operating an automobile or machinery, the patient should be cautioned accordingly.

Tofranil-PM may enhance the CNS depressant effects of alcohol. Therefore, it should be borne in mind that the dangers inherent in a suicide attempt or accidental overdosage with the drug may be increased for the patient who uses excessive amounts of alcohol. (See PRECAUTIONS.)

Usage in Children: Tofranil-PM should not be used in children of any age because of the increased potential for acute overdosage due to the high unit potency (75 mg, 100 mg, 125 mg, and 150 mg). Each capsule contains imipramine pamoate equivalent to 75mg, 100 mg, 125 mg, or 150mg imipramine hydrochloride.

PRECAUTIONS

General

An ECG recording should be taken prior to the initiation of larger-than-usual doses of imipramine pamoate and at appropriate intervals thereafter until steady state is achieved. (Patients with any evidence of cardiovascular disease require cardiac surveillance at all dosage levels of the drug. See WARNINGS.) Elderly patients and patients with cardiac disease or a prior history of cardiac disease are at special risk of developing the cardiac abnormalities associated with the use of imipramine pamoate. It should be kept in mind that the possibility of suicide in seriously depressed patients is inherent in the illness and may persist until significant remission occurs. Such patients should be carefully supervised during the early phase of treatment with imipramine pamoate and may require hospitalization. Prescriptions should be written for the smallest amount feasible.

Hypomanic or manic episodes may occur, particularly in patients with cyclic disorders. Such reactions may necessitate discontinuation of the drug. If needed, imipramine pamoate may be resumed in lower dosage when these episodes are relieved. Administration of a tranquilizer may be useful in controlling such episodes.

An activation of the psychosis may occasionally be observed in schizophrenic patients and may require reduction of dosage and the addition of a phenothiazine.

Concurrent administration of imipramine pamoate with electroshock therapy may increase the hazards: such treatment should be limited to those patients for whom it is essential, since there is limited clinical experience.

Patients taking imipramine pamoate should avoid excessive exposure to sunlight since there have been reports of photosensitization.

Both elevation and lowering of blood sugar levels have been reported with imipramine pamoate use.

Imipramine pamoate should be used with caution in patients with significantly impaired renal or hepatic function.

Patients who develop a fever and a sore throat during therapy with imipramine pamoate should have leukocyte and differential blood counts performed.

Imipramine pamoate should be discontinued if there is evidence of pathological neutrophil depression.

Prior to elective surgery, imipramine pamoate should be discontinued for as long as the clinical situation will allow.

Drug Interactions

Drugs Metabolized by P450 2D6: The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the Caucasian population (about 7%- 10% of Caucasians are so-called "poor metabolizers"); reliable estimates of the prevalence of reduced P450

2D6 isozyme activity among Asian, African, and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8-fold increase in plasma AUC of the TCA).

In addition, certain drugs inhibit the activity of this isozyme and make normal metabolizers resemble poor metabolizers. An individual who is stable on a given dose of TCA may become abruptly toxic when given one of these inhibiting drugs as concomitant therapy. The drugs that inhibit cytochrome P450 2D6 include some that are not metabolized by the enzyme (quinidine; cimetidine) and many that are substrates for P450 206 (many other antidepressants, phenothiazines, and the Type 1 C antiarrhythmics propafenone and flecainide). While all the selective serotonin reuptake inhibitors (SSRIs), e.g., fluoxetine, sertraline, and paroxetine, inhibit P450 2D6, they may vary in the extent of inhibition. The extent to which SSRI-TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the co-administration of TCAs with any of the SSRIs and also in switching from one class to the other. Of particular importance, sufficient time must elapse before initiating TCA treatment in a patient being withdrawn from fluoxetine, given the long half-life of the parent and active metabolite (at least 5 weeks may be necessary).

Concomitant use of tricyclic antidepressants with drugs that can inhibit cytochrome P45O 2D6 may require lower doses than usually prescribed for either the tricyclic antidepressant or the other drug. Furthermore, whenever one of these other drugs is withdrawn from co-therapy, an increased dose of tricyclic antidepressant may be required. It is desirable to monitor TCA plasma levels whenever a TCA is going to be co-administered with another drug known to be an inhibitor of P450 2D6.

The plasma concentration of imipramine may increase when the drug is given concomitantly with hepatic enzyme inhibitors (e.g., cimetidine, fluoxetine) and decrease by concomitant administration with hepatic enzyme inducers (e.g., barbiturates, phenytoin), and adjustment of the dosage of imipramine may therefore be necessary.

In occasional susceptible patients or in those receiving anticholinergic drugs (including antiparkinsonism agents) in addition, the atropine-like effects may become more pronounced (e.g., paralytic ileus). Close supervision and careful adjustment of dosage is required when imipramine pamoate is administered concomitantly with anticholinergic drugs.

Avoid the use of preparations, such as decongestants and local anesthetics, that contain any sympathomimetic amine (e.g., epinephrine, norepinephrine), since it has been reported that tricyclic antidepressants can potentiate the effects of catecholamines.

Caution should be exercised when imipramine pamoate is used with agents that lower blood pressure. Imipramine pamoate may potentiate the effects of CNS depressant drugs.

Patients should be warned that imipramine pamoate may enhance the CNS depressant effects of alcohol. (See WARNINGS.)

Pregnancy

Animal reproduction studies have yielded inconclusive results. (See also ANIMAL PHARMACOLOGY & TOXICOLOGY.)

There have been no well-controlled studies conducted with pregnant women to determine the effect of imipramine on the fetus. However, there have been clinical reports of congenital malformations associated with the use of the drug. Although a causal relationship between these effects and the drug could not be established, the possibility of fetal risk from the maternal ingestion of imipramine cannot be excluded. Therefore, imipramine should be used in women who are or might become pregnant only if the clinical condition clearly justifies potential risk to the fetus.

Nursing Mothers

Limited data suggest that imipramine is likely to be excreted in human breast milk. As a general rule, a woman taking a drug should not nurse since the possibility exists that the drug may be excreted in breast milk and be harmful to the child.

Pediatric Use

See WARNINGS.

ADVERSE REACTIONS

Note: Although the listing which follows includes a few adverse reactions which have not been reported with this specific drug, the pharmacological similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when imipramine is administered.

Cardiovascular: Orthostatic hypotension, hypertension, tachycardia, palpitation, myocardial infarction,

arrhythmias, heart block, ECG changes, precipitation of congestive heart failure, stroke.
Psychiatric: Confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnisand nightmares; hypomania; exacerbation of psychosis.
Neurological: Numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures, alterations in EEG patterns; tinnitus.
Anticholinergic: Dry mouth, and, rarely, associated sublingual adenitis; blurred vision, disturbances of accommodation, mydriasis; constipation, paralytic ileus; urinary retention, delayed micturition, dilation of the urinary tract.
Allergic: Skin rash, petechiae, urticaria, itching, photosensitization; edema (general or of face and tongue); drug fever; cross-sensitivity with desipramine.
Hematologic: Bone marrow depression including agranulocytosis; eosinophilia; purpura; thrombocytopenia.
Gastrointestinal: Nausea and vomiting, anorexia, epigastric distress, diarrhea; peculiar taste, stomatitis, abdominal cramps, black tongue.
Endocrine: Gynecomastia in the male; breast enlargement and galactorrhea in the female; increased or decreased libido, impotence; testicular swelling; elevation or depression of blood sugar levels; inappropriate antidiuretic hormone (ADH) secretion syndrome.
Other: Jaundice (simulating obstructive); altered liver function; weight gain or loss; perspiration; flushing; urinary frequency; drowsiness, dizziness, weakness and fatigue; headache; parotid swelling; alopecia; proneness to falling.
Withdrawal Symptoms: Though not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache and malaise.

DOSAGE AND ADMINISTRATION

The following recommended dosages for Tofranil-PM should be modified as necessary by the clinical response and any evidence of intolerance.
Initial Adult Dosage:
Outpatients —Therapy should be initiated at 75 mg/day. Dosage may be increased to 150 mg/day which is the dose level at which optimum response is usually obtained. If necessary, dosage may be increased to 200 mg/day.

Dosage higher than 75 mg/day may also be administered on a once-a-day basis after the optimum dosage and tolerance have been determined. The daily dosage may be given at bedtime. In some patients it may be necessary to employ a divided-dose schedule.

As with all tricyclics, the antidepressant effect of imipramine may not be evident for one to three weeks in some patients.
Hospitalized Patients — Therapy should be initiated at 100-150 mg/day and may be increased to 200 mg/day. If there is no response after two weeks, dosage should be increased to 250-300 mg/day.

Dosage higher than 150mg/day may also be administered on a once-a-day basis after the optimum dosage and tolerance have been determined. The daily dosage may be given at bedtime. In some patients it may be necessary to employ a divided-dose schedule.

As with all tricyclics, the antidepressant effect of imipramine may not be evident for one to three weeks in some patients.
Adult Maintenance Dosage: Following remission, maintenance medication may be required for a longer period of time at the lowest dose that will maintain remission after which the dosage should gradually be decreased.

The usual maintenance dosage is 75-1 50 mg/day. The total daily dosage can be administered on a once-a-day basis, preferably at bedtime. In some patients it may be necessary to employ a divided-dose schedule.

In cases of relapse due to premature withdrawal of the drug, the effective dosage of imipramine should be reinstituted.
Adolescent and Geriatric Patients: Therapy in these age groups should be initiated with Tofranil®, brand of imipramine hydrochloride, tablets at a total daily dosage of 25-50 mg, since Tofranil-PM capsules are not available in these strengths. Dosage may be increased according to response and tolerance, but it is generally unnecessary to exceed 100 mg/day in these patients. Tofranil-PM capsules may be used when total daily dosage is established at 75 mg or higher.

The total daily dosage can be administered on a once-a-day basis, preferably at bedtime. In some patients it may be necessary to employ a divided-dose schedule.

As with all tricyclics, the antidepressant effect of imipramine may not be evident for one to three weeks in some patients.

Adolescent and geriatric patients can usually be maintained at lower dosage. Following remission, maintenance medication may be required for a longer period of time at the lowest dose that will maintain remission after which the dosage should gradually be decreased.

The total daily maintenance dosage can be administered on a once-a-day basis, preferably at bedtime.

In some patients it may be necessary to employ a divided-dose schedule.

In cases of relapse due to premature withdrawal of the drug, the effective dosage of imipramine should be reinstituted.

OVERDOSAGE

Deaths may occur from overdosage with this class of drugs. Multiple drug ingestion (including alcohol) is common in deliberate tricyclic overdose. As the management is complex and changing, it is recommended that the physician contact a poison control center for current information on treatment. Signs and symptoms of toxicity develop rapidly after tricyclic overdose. Therefore, hospital monitoring is required as soon as possible.

Children have been reported to be more sensitive than adults to an acute overdosage of imipramine pamoate. An acute overdose of any amount in infants or young children, especially, must be considered serious and potentially fatal.

Manifestations

These may vary in severity depending upon factors such as the amount of drug absorbed, the age of the patient, and the interval between drug ingestion and the start of treatment. Critical manifestations of overdose include cardiac dysrhythmias, severe hypotension, convulsions, and CNS depression including coma. Changes in the electrocardiogram, particularly in QRS axis or width, are clinically significant indicators of tricyclic toxicity.

Other CNS manifestations may include drowsiness, stupor, ataxia, restlessness, agitation, hyperactive reflexes, muscle rigidity, athetoid and choreiform movements.

Cardiac abnormalities may include tachycardia, and signs of congestive failure. Respiratory depression, cyanosis, shock, vomiting, hyperpyrexia, mydriasis, and diaphoresis may also be present.

Management

Obtain an ECG and immediately initiate cardiac monitoring. Protect the patient's airway, establish an intravenous line, and initiate gastric decontamination. A minimum of 6 hours of observation with cardiac monitoring and observation for signs of CNS or respiratory depression, hypotension, cardiac dysrhythmias and/or conduction blocks, and seizures is necessary. If signs of toxicity occur at any time during this period, extended monitoring is required. There are case reports of patients succumbing to fatal dysrhythmias late after overdose; these patients had clinical evidence of significant poisoning prior to death and most received inadequate gastrointestinal decontamination. Monitoring of plasma drug levels should not guide management of the patient.

Gastrointestinal Decontamination*:* All patients suspected of tricyclic overdose should receive gastrointestinal decontamination. This should include large volume gastric lavage followed by activated charcoal. If consciousness is impaired, the airway should be secured prior to lavage. Emesis is contraindicated.

Cardiovascular: A maximal limb-lead QRS duration of > 0.10 seconds may be the best indication of the severity of the overdose. Intravenous sodium bicarbonate should be used to maintain the serum pH in the range of 745 to 7.55. If the pH response is inadequate, hyperventilation may also be used. Concomitant use of hyperventilation and sodium bicarbonate should be done with extreme caution, with frequent pH monitoring. A pH >7.60 or a Pco2 <20 mmHg is undesirable. Dysrhythmias unresponsive to sodium bicarbonate therapy/hyperventilation may respond to lidocaine, bretylium, or phenytoin. Type 1 A and 1 C antiarrhythmics are generally contraindicated (e.g., quinidine, disopyramide, and procainamide).

In rare instances, hemoperfusion may be beneficial in acute refractory cardiovascular instability in patients with acute toxicity. However, hemodialysis, peritoneal dialysis, exchange transfusions, and forced diuresis generally have been reported as ineffective in tricyclic poisoning.

CNS: In patients with CNS depression, early intubation is advised because of the potential for abrupt deterioration. Seizures should be controlled with benzodiazepines, or if these are ineffective, other anticonvulsants (e.g., phenobarbital, phenytoin). Physostigmine is not recommended except to treat life-threatening symptoms that have been unresponsive to other therapies, and then only in consultation with

a poison control center.

Psychiatric Follow-up: Since overdosage is often deliberate, patients may attempt suicide by other means during the recovery phase. Psychiatric referral may be appropriate.

Pediatric Management: The principles of management of child and adult overdosages are similar. It is strongly recommended that the physician contact the local poison control center for specific pediatric treatment.

HOW SUPPLIED

Capsules 75 mg—coral (imprinted black Geigy 20) equivalent to 75 mg imipramine hydrochloride

Bottles of 30 NDC 0406-9923-03
Bottles of 100 NDC 0406-9923-01

Capsules 100 mg—dark yellow/coral (imprinted black Geigy 40) equivalent to 100 mg imipramine hydrochloride

Bottles of 30 NDC 0406-9924-03
Bottles of 100 NDC 0406-9924-01

Capsules 125mg—ivory/coral (imprinted black Geigy 45) equivalent to 125 mg imipramine hydrochloride

Bottles of 30 NDC 0406-9925-03
Bottles of 100 NDC 0406-9925-01

Capsules 150 mg — coral (imprinted black Geigy 22) equivalent to 150 mg imipramine hydrochloride

Bottles of 30 NDC 0406-9926-03
Bottles of 100 NDC 0406-9926-01

Do not store above 86°F (30°C).
Dispense in tight container (USP).

ANIMAL PHARMACOLOGY & TOXICOLOGY

A. *Acute:* Oral LD_{50}:

Mouse	2185 mg/kg
Rat(F)	1142 mg/kg
(M)	1807 mg/kg
Rabbit	1016 mg/kg
Dog	693 mg/kg (Emesis ED_{50})

B. *Subacute*:

Two three-month studies in dogs gave evidence of an adverse drug effect on the testes, but only at the highest dose level employed, i.e., 90 mg/kg (10 times the maximum human dose). Depending on the histological section of the testes examined, the findings consisted of a range of degenerative changes up to and including complete atrophy of the seminiferous tubules, with spermatogenesis usually arrested.

Human studies show no definitive effect on sperm count, sperm motility, sperm morphology or volume of ejaculate.

Rat

One three-month study was done in rats at dosage levels comparable to those of the dog studies. No adverse drug effect on the testes was noted in this study, as confirmed by histological examination.

C. *Reproduction*/*Teratogenic:*

Oral: Imipramine pamoate was fed to male and female albino rats for 26 weeks through two breeding cycles at dose levels of 15 mg/ kg/day and 40 mg/kg/day (equivalent to 21/2 and 7 times the maximum human dose).

No abnormalities which could be related to drug administration were noted in gross inspection. Autopsies performed on pupa from the second breeding likewise revealed no pathological changes in organs or tissues; however, a decrease in mean litter size from both matings was noted in the drug-treated groups and significant growth suppression occurred in the nursing pupa of both sexes in the high group as well as in the females of the low-level group. Finally, the lactation index (pups weaned divided by number left to nurse) was significantly lower in the second litter of the high-level group.

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